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Adolescent Reproductive Events and Subsequent Breast Cancer Risk

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ABSTRACT

Objectives. This study investigated the relationship between reproductive events during adolescence and subsequent breast cancer risk.

Methods. Logistic regression models used self-reported data from 862 case patients and 790 controls in the Carolina Breast Cancer Study.

Results. Miscarriage, induced abortion, and full-term pregnancy before 20 years of age were not associated with breast cancer. Among premenopausal women, breast-feeding before 20 years of age was inversely associated with disease. Oral contraceptive use before 18 years of age was positively associated with disease risk among African American women only.

Conclusions. Pregnancy during adolescence does not appear to influence breast cancer risk, but breast-feeding may. A possible increased breast cancer risk among African American women who used oral contraceptives as adolescents warrants further study. (*Am J Public Health.* 1999;89:1244–1247)

Reproductive events are among the most well established of breast cancer risk factors.[1] Often hypothesized to act by modifying endogenous hormone levels,[2] the occurrence of such events during adolescence can have different effects on risk in that the adolescent and adult hormonal milieus can be quite different.[3] Adolescent reproductive exposures also may be markers for other breast cancer risk factors, such as socioeconomic status (SES), or highly correlated with other aspects of exposure that are related to disease risk.

We explored the relationships of full-term pregnancy, breast-feeding, miscarriage, induced abortion, and oral contraceptive use during adolescence with subsequent breast cancer risk by analyzing data from the Carolina Breast Cancer Study, a population-based case–control investigation. We also examined potential effect modification by age, race, and menopausal status.

Methods

The Carolina Breast Cancer Study was a population-based, case–control study of breast cancer in a contiguous 24-county region of central and eastern North Carolina.[4] Women aged 20 to 74 years with a first invasive, primary breast cancer diagnosis between May 1993 and May 1996 were eligible; African American case patients and patients younger than 50 years at diagnosis were oversampled to increase the numbers in these subgroups. Sampling fractions and randomized recruitment techniques were used in selecting case patients.[5,6] The same methods were used to sample controls from Division of Motor Vehicle records (if the individuals were younger than 65 years) and Medicare records (if the individuals were 65 years or older); these individuals were frequency matched to the case patient age–race distribution. All study interviews were conducted in person. Response rates, calculated among women who were eligible and could be located, were 77% among case patients and 68% among controls.[7]

We explored the relationship of breast cancer with adolescent occurrence of a first full-term pregnancy (gestation of 7 months or more), breast-feeding, miscarriage (gestation of less than 7 months), induced abortion, and

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This paper was accepted March 5, 1999.

TABLE 1—Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Age at First Lactation and Breast Cancer Risk: Carolina Breast Cancer Study, 1993–1996

	Premenopausal			Postmenopausal		
	Case Patients	Controls	OR[a] (95% CI)	Case Patients	Controls	OR[a] (95% CI)
Never breast-fed	187	146	1.0	207	197	1.0
First breast-fed before 20 years of age	5	15	0.2 (0.1, 0.6)	58	66	0.8 (0.5, 1.2)
Lifetime lactation duration <1 year	4	10	0.3 (0.1, 1.0)	25	37	0.6 (0.4, 1.1)
Lifetime lactation duration ≥1 year	1	5	0.1 (0.0, 0.8)	33	29	1.0 (0.6, 1.7)
First breast-fed at 20 years or older	112	95	0.8 (0.6, 1.2)	98	128	0.7 (0.5, 1.0)
Lifetime lactation duration <1 year	68	62	0.8 (0.5, 1.2)	62	79	0.7 (0.5, 1.1)
Lifetime lactation duration ≥1 year	44	33	0.9 (0.6, 1.6)	35	44	0.7 (0.4, 1.1)
First full-term birth before 20 years of age						
Never breast-fed	74	52	1.0	68	61	1.0
First breast-fed before 20 years of age	5	15	0.2 (0.1, 0.6)	57	66	0.7 (0.4, 1.1)
First breast-fed at 20 years or older	4	10	0.3 (0.1, 0.9)	66	12	0.5 (0.2, 1.3)

Note. Data are restricted to parous women with known or imputed menopausal status.
[a]Adjusted for race and age at diagnosis–selection, as well as sampling design.

use of oral contraceptives (duration of 3 months or more). Adolescence was initially defined as the period between 10 and 19 years of age, but the range was further divided if sample size permitted. Questions directly assessed age at first occurrence of the reproductive event or exposure. Analyses of breast-feeding were restricted to parous women; analyses of miscarriage or induced abortion were conducted regardless of, as well as contingent on, gravidity status. An analysis comparing adolescent induced abortion with other adolescent pregnancy outcomes (i.e., miscarriage or full-term pregnancy during adolescence) also was conducted. Analyses of induced abortion and oral contraceptive use were restricted to women younger than 50 years because of the very rare occurrence of these exposures during adolescence among older women.

The 5 study exposures were examined as potential confounders of one another, as were other established or suspected breast cancer risk factors, including age at menarche, body mass, number of full-term births, attained education, and breast cancer history in a first-degree relative. Other adolescent exposures, including comparative body size at 10 years of age, physical activity at 12 years of age, and age at initiation of cigarette smoking and alcohol consumption, also were considered. Methods previously employed by Newcomb et al.[8] were used in imputing menopausal status for women who had undergone a hysterectomy but had at least 1 remaining ovary. Race (African American vs others), menopausal status (premenopausal vs postmenopausal), and age at diagnosis–selection (younger than 50 years vs 50 years or older) were explored as possible effect modifiers.

Logistic regression models with terms for age (modeled in 5-year intervals), race, and an offset to account for the sampling design were used to determine relative odds of disease.[9,10] In no instance did inclusion of a potential confounder change the odds ratio (OR) of interest by more than 15% (our confounding criterion); thus, we present odds ratios adjusted only for the design variables. Effect modification was deemed present if stratum-specific odds ratios differed 2-fold or more. Effect modification by age was not explored for induced abortion or oral contraceptive use because analyses excluded individuals 50 years and older; in analyses of miscarriage and induced abortion restricted to nulliparous women, evaluation of effect modification by race was not possible owing to the small numbers of women experiencing such events. We examined whether lifetime duration of breast-feeding or time since most recent use of oral contraceptives influenced the associations of each adolescent exposure with breast cancer risk. In an attempt to disentangle the relationships of adolescent full-term pregnancy and breast-feeding with breast cancer, we examined the relationship of breast-feeding and breast cancer risk among women with a first full-term pregnancy before 20 years of age.

Results

Although our goal was to accrue approximately equal numbers of participants for each race and age category, our final sample contained fewer African American women (335 case patients and 332 controls, as compared with 527 White case patients and 458 controls) and fewer older women (356 case patients 50 years and older and 383 controls, as compared with 506 case patients younger than 50 years and 407 controls). As expected, case patients were more likely than controls to report a family history of breast cancer, an earlier age at menarche, and fewer full-term pregnancies (data not shown).

Relative to women with a first full-term pregnancy occurring between 20 and 29 years of age, those with a first full-term pregnancy before 18 years of age (OR = 1.1, 95% confidence interval [CI] = 0.8, 1.5) or at 18 or 19 years of age (OR = 1.0, 95% CI = 0.8, 1.4) were not at reduced breast cancer risk. Among parous, premenopausal women, breast-feeding before 20 years of age, relative to no history of breast-feeding, was associated with a substantial risk reduction (OR = 0.2, 95% CI = 0.1, 0.6); however, this result was based on small numbers of women reporting lactation during their teen years (Table 1). This inverse relationship persisted when lifetime duration of lactation was considered and when analyses were restricted to women with a first full-term pregnancy before 20 years of age. In the latter analysis, adjustment for lifetime number of full-term pregnancies and restriction to women with parity of 2 or greater produced similar results (data not shown).

Neither miscarriage nor induced abortion before 20 years of age, relative to no history of either event, conferred a meaningful increase in risk (Table 2). The absence of a relationship persisted in separate analyses restricted to gravid, parous, or nulliparous women. Comparison of induced abortions with other adolescent pregnancy outcomes also suggested no association.

African American women who used oral contraceptives before 18 years of age were at elevated risk of breast cancer relative to those who had never used oral contraceptives (OR = 2.0, 95% CI = 1.0, 4.3)

TABLE 2—Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Age at First Premature Pregnancy Termination and Breast Cancer Risk: Carolina Breast Cancer Study, 1993–1996

	All Women			Nulliparous Women			Gravid Women			Parous Women		
	Case Patients	Controls	OR[a] (95% CI)	Case Patients	Controls	OR[a] (95% CI)	Case Patients	Controls	OR[a] (95% CI)	Case Patients	Controls	OR[a] (95% CI)
Age at first miscarriage, y												
Never	637	548	1.0	111	72	1.0	546	487	1.0	526	476	1.0
<20	40	34	1.0 (0.6, 1.6)	6	5	0.9 (0.3, 3.5)	40	34	1.0 (0.6, 1.7)	34	29	1.1 (0.6, 1.8)
≥20	177	186	0.8 (0.6, 1.0)	16	10	0.9 (0.4, 2.3)	177	186	0.8 (0.7, 1.1)	161	176	0.8 (0.9, 1.1)
Age at first induced abortion, y[b]												
Never	416	344	1.0	72	43	1.0	355	309	1.0	344	301	1.0
<20	19	11	1.2 (0.6, 2.7)	5	2	1.3 (0.2, 9.7)	19	11	1.3 (0.6, 2.9)	14	9	1.2 (0.5, 2.9)
≥20	65	45	1.1 (0.7, 1.7)	14	6	1.2 (0.4, 3.9)	65	45	1.2 (0.8, 1.8)	51	39	1.1 (0.7, 1.8)
Outcome of first adolescent pregnancy[b,c]												
First full-term pregnancy or miscarriage before 20 years	...	...	...	...	...	...	250	252	1.0	244	247	1.0
First induced abortion before 20 years	...	...	...	...	...	...	19	11	1.2 (0.5, 2.9)	14	9	1.1 (0.4, 2.8)

[a]Adjusted for race and age at diagnosis–selection, as well as sampling design.
[b]Restricted to women younger than 50 years at diagnosis–selection.
[c]Restricted to women who had a pregnancy before 20 years of age.

(Table 3). Among White women, no such relationship was observed. Exclusion of women whose first use occurred during adolescence but after a full-term pregnancy did not change the results (data not shown). Among African American women who used oral contraceptives during adolescence, higher risks were observed for current users and those who discontinued use within the 10 years before diagnosis–selection (Table 3).

Discussion

In this population-based case–control study of North Carolina women, adolescent pregnancies neither increased nor decreased breast cancer risk. Among premenopausal women, breast-feeding before 20 years of age was inversely associated with disease risk. Use of oral contraceptives before 18 years of age was positively associated with disease risk only among African American women.

Our finding of no breast cancer risk reduction with a first full-term pregnancy before 18 years of age was observed in one[11] of two[11,12] previous studies that explored the relationship. We expected an inverse association because first full-term pregnancies at young ages are generally assumed to reduce breast cancer risk owing to early breast cell differentiation.[13] The considerable reduction in breast cancer risk seen here among premenopausal women who breast-fed as ado-

TABLE 3—Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Age at First Oral Contraceptive (OC) Use and Breast Cancer, Among Women Younger Than 50 Years: Carolina Breast Cancer Study, 1993–1996

	White			African American		
	Case Patients	Controls	OR[a] (95% CI)	Case Patients	Controls	OR[a] (95% CI)
Never used OCs	41	34	1.0	35	45	1.0
First OC use before 18 years of age	37	33	0.9 (0.4, 1.7)	36	20	2.0 (1.0, 4.3)
First OC use at 18 or 19 years of age	85	67	1.1 (0.6, 1.9)	39	35	1.4 (0.8, 2.8)
First OC use before 20 years of age						
Regardless of TSLU	122	100	1.0 (0.6, 1.7)	75	55	1.6 (0.9, 2.9)
TSLU <10 years[b]	47	34	1.0 (0.5, 2.1)	33	16	2.2 (1.0, 5.3)
TSLU ≥10 years	75	66	1.0 (0.6, 1.8)	42	39	1.4 (0.8, 2.7)
First OC use at 20 years or older						
Regardless of TSLU	166	102	1.4 (0.8, 2.3)	65	71	1.2 (0.7, 2.1)
TSLU <10 years[b]	47	26	1.5 (0.8, 3.0)	23	19	1.7 (0.8, 3.7)
TSLU ≥10 years	119	76	1.3 (0.8, 2.3)	42	52	1.1 (0.6, 2.0)

Note. TSLU = time since last use.
[a]Adjusted for race and age at diagnosis–selection, as well as sampling design.
[b]Includes current users.

lescents also has been observed in another study.[8] Breast-feeding, regardless of timing, may reduce risk through breast cell differentiation and involution over and above that of pregnancy, as well as by elimination of carcinogens via breast milk.[14,15]

Results of analyses of adolescent miscarriage and induced abortion, hypothesized to increase breast cancer risk as a result of breast cell proliferation without differentiation,[16] have been quite varied.[17–20] This may be due to the use of different reference categories and parity restrictions. We conducted a variety of analyses, including those used by other investigators[17–20] (data not shown), yet none produced evidence of an association of breast cancer with adolescent miscarriage and induced abortion. Reporting error also may influence analyses of induced abortion.[21] The extent of such error will probably vary across studies for several reasons, including the legality of the procedure as well as the ages and religious beliefs of participants. Our analysis comparing adolescent induced abortion with other potential pregnancy outcomes has not been presented previously; we believe it may be most relevant, however, because it directly reflects the choice faced by pregnant teens.

Adolescent oral contraceptive use can substantially increase levels of circulating ovarian hormones, because menstrual cycles during adolescence are often anovulatory.[3] Hence, adolescent oral contraceptive use is hypothesized to increase breast cancer risk. A large pooled analysis indicated that first use of oral contraceptives before 20 years of age conferred, of all initiation ages, the greatest increase in risk, although the magnitude was small and varied by amount of time since most recent use.[22] The only study other than ours to examine the relationship specifically among African American women also observed a substantially elevated breast cancer risk.[23] There is little reason to believe that this association should differ by race; therefore, other factors may have influenced our observation of effect modification, including the possibility of nonresponse bias. Differences in educational attainment between users and nonusers of oral contraceptives were more extreme for African American participants than for White participants, suggesting that inadequate control of confounding, perhaps for SES, might have produced this discrepancy. However, adjustment for education, current income, and a measure of adolescent SES (head of household's occupation) did not influence the results.

Given that many adolescent girls are sexually active, the relationship of reproductive events and exposures during the teen years with future breast cancer risk is of potential public health importance. A possible increase in breast cancer among women who used oral contraceptives during adolescence, particularly African Americans, warrants further study. □

Contributors

All authors contributed to the development of hypotheses, development of analysis strategies, and preparation of the manuscript. P.M. Marcus analyzed the data and wrote most of the manuscript. D.D. Baird contributed to the design of variables. R.C. Millikan, P.G. Moorman, B. Qaqish, and B. Newman planned the Carolina Breast Cancer Study. B. Newman conceptualized the Carolina Breast Cancer Study and obtained funding. R.C. Millikan, P.G. Moorman, and B. Newman directed and managed the Carolina Breast Cancer Study.

Acknowledgments

This work was funded in part through the following National Cancer Institute (NCI) grants: T32-CA09330 (Cancer Training Grant), R25-CA57726 (Cancer Prevention and Control Pre-Doctoral Fellowship), and P50-CA58223 (SPORE in Breast Cancer). Additional support was received from the NCI Cancer Prevention and Control Fellowship Program.

This work was approved by the Public Health Institutional Review Board of the University of North Carolina School of Medicine. All subjects consented to be interviewed.

We wish to thank the Carolina Breast Cancer Study interviewers, Carolyn Dunmore, Dianne Mattingly, Cherryl Robinson, Theresa Nalevaiko, and Patricia Plummer. We also thank Jessica Tse and Dr Beverly Rockhill for their data management and statistical assistance.

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